(19) Eur päisches Patentamt
European Patent Office
Offic européen des brevets

(11) Publication number: **0 045 655**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 81303545.8

(22) Date of filing: 03.08.81

(51) Int. Cl.³: A 61 K 9/00

(30) Priority: 04.08.80 US 174957

(43) Date of publication of application:
10.02.82 Bulletin 82/6

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: MERCK & CO. INC.
126, East Lincoln Avenue P.O. Box 2000
Rahway, New Jersey 07065(US)

(72) Inventor: Lo, Pak-Kan Albert
17 Lombardi Street
Edison New Jersey 08817(US)

(72) Inventor: Williams, James B.
4 Coventry Drive
Freehold New Jersey 07728(US)

(74) Representative: Crampton, Keith John Allen et al,
D YOUNG & CO 10 Staple Inn
London WC1V 7RD(GB)

(54) **Solubilization of ivermectin in water.**

(57) Ivermectin, an antiparasitic agent which is insoluble and unstable in water, is solubilized by the formation of colloidal particles, called micelles, with surface-active agents as solubilizers and stabilized by using water-miscible organic cosolvents and/or appropriate substrates in the aqueous formulation. The liquid formulations are suitable for use as parenteral or oral administration for the treatment of parasitic infections.

EP 0 045 655 A2

Croydon Printing Company Ltd.

SOLUBILIZATION OF IVERMECTIN IN WATER

Ivermectin is a new and very potent antiparasitic, and particularly anthelmintic, agent that is useful against a broad spectrum of endoparasites and ectoparasites in mammals as well as having agricultural uses against various parasites found in and on crops and in soil. Ivermectin is disclosed in U.S. Patent 4,199,569, issued 22 April, 1980 to Chabala and Fisher. Ivermectin is a mixture, in the ratio of approximately 80:20 of 22,23-dihydro C-076 B1a and B1b. In administering Ivermectin to animals it is most convenient for parenteral formulations to use an aqueous solution. Non-aqueous solutions tend to cause irritation and tissue damage at the injection site; precipitate the active ingredient at the injection site; have higher viscosity and poorer syringability; and generally have a higher cost. Aqueous liquid formulations for oral use are also preferred over non-aqueous formulations because non-aqueous solvents tend to have an unacceptable taste.

Thus, it is desirable to prepare an aqueous liquid formulation of Ivermectin. However, Ivermectin has very poor solubility in water, at a level of about 0.005 mg per ml at room temperature.

Ivermectin can be solubilized using surface-active agents as solubilizers. This results in the formation of micelles, or minute colloidal particles which surround the Ivermectin

molecule, isolating it from the water, but forming a clear solution in the water. Such a solution does contain sufficient active ingredient in order to prepare liquid formulations, for oral or parenteral use. However, it was discovered that such micelle formulations were unstable and the Ivermectin degraded at such a rate as to render the shelf life inadequate for a commercial preparation.

It was unexpectedly discovered during the investigation of this instability that the use of certain cosolvents and/or substrates would reduce the instability and result in an aqueous liquid solution which is suitable for parenteral or oral administration, and which had adequate shelf life such that a viable commercial preparation was afforded.

The present invention concerns the solubilization and stabilization of Ivermectin using surface-active agents to dissolve the Ivermectin, and certain cosolvents and substrates to stabilize the thus formed micelle solution, and this invention provides a stabilized aqueous formulation comprising Ivermectin in a solution of a surface-active agent and water and including one or more water-miscible organic co-solvents suitable for parenteral or oral administration, and/or one or more substrates also suitable for parenteral or oral administration. The stabilized solution can be used to prepare parenteral and oral formulations.

The cosolvent and the substrate used in the formulations of the present invention individually reduce the instability of the Ivermectin solution: however, the combination of the cosolvent and the substrate is surprisingly found to increase the stability of the solution even further.

The aqueous Ivermectin solution is initially formed by dissolving the Ivermectin in a pharmacologically acceptable surface-active agent. A different surface-active agent will be used depending upon whether the final formulation is to be for parenteral or oral use.

For parenteral use a pharmacologically acceptable non-ionic surface-active agent will be used. Examples of such non-ionic surface active agents are polyoxyethylated vegetable oils,

polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate and polyoxyethylenesorbitan monooleate (also known as polysorbate 80 or under the trade mark Tween 80). The preferred surface-active agent is polysorbate 80.

For oral use, a pharmacologically acceptable non-ionic surfactant or an anionic surface-active agent will be used. The non-ionic surface-active agents mentioned for the parenteral formulation may also be used for the oral formulation, and again polysorbate 80 is the preferred non-ionic surface-active agent. An example of an anionic surface-active agent is dioctylsodium sulfosuccinate (also known as Aerosol OT), which is the preferred anionic surface-active agent.

The aqueous solution of Ivermectin and the surface-active agent is prepared by dissolving the Ivermectin in the surface-active agent such that the surface-active agent will constitute from 4 to 25% w/v of the final solution. The Ivermectin is present in different amounts for parenteral and oral uses. For parenteral formulations the Ivermectin is present at from 0.1 to 7.5% w/v and for oral formulations the Ivermectin is present in from 0.01 to 2.0% w/v. Water may then be added to the solution of surface-active agent to form a clear solution.

The cosolvents are water-miscible organic solvents that are suitable for parenteral or oral administration. Examples of such cosolvents are glycerol formal, propylene glycol, glycerine and polyethylene glycol. The preferred solvent for parenteral administration is glycerol formal and for oral administration is propylene glycol. The cosolvents are added to the final formulation to the extent of 10 to 40% v/v of the final formulation.

The substrates which are used to stabilize the formulation, either alone or in combination with the cosolvent, include benzyl alcohol, lidocain, parabens and choline. Benzyl alcohol and lidocaine are the preferred substrates and both have been used in a single formulation with acceptable results. The substrates are present in the final formulations at a concentration of from 1 to 5% w/v. Benzyl alcohol is specifically present at about 1 to 5% v/v and lidocaine is present at about 1 t 4% w/v.

The preferred process for preparing the formulation is to combine the Ivermectin in a mixture of the surface active agent, the cosolvent and the substrate. At this time also buffering agents and other adjuvents which assist in the final formulation may be added. Water is then added to the desired volume, or almost the desired volume, and the pH adjusted, if necessary, to a range of 6.0 and 6.5 for optimum stability. The final volume is adjusted to the desired amount and the solution sterilized by autoclaving or membrane filtration.

The stability of the Ivermectin aqueous solution is thus greatly improved through the use of the above-described cosolvents and substrates. Without such cosolvents and substrates, the solution of Ivermectin formed by combining the drug in a surfactant and adding water is observed to have a 50% stability per month at room temperature. That is, 50% of the Ivermectin is lost after only one month. By combining a cosolvent or a substrate with the surfactant, the stability is seen to dramatically increase to about 10% in 2 to 3 months; or about 5% loss of Ivermectin activity per month. When both the cosolvent and the substrate are used in the surfactant formulation the stability of the resultant aqueous formulation is seen to even more dramatically increase its stability to less than 5% in 2 to 3 years.

The reason behind this dramatic and unexpected stabilizing effects resulting from the use of the cosolvent and the substrate are not completely understood. While this theory is not to be taken as binding, it appears that in the initial micelle formation with the Ivermectin and the substrate, water is still able to penetrate the micelle or otherwise contact the Ivermectin, even though it is surrounded by the surface-active agent. The cosolvent and the substrate apparently displace the water of hydration of the micelle and further isolate the Ivermectin from the water that contacts the outside surface of the micelle, thus reducing the reaction of the water upon the Ivermectin and increasing the stability of the resultant solution.

The resultant solution thus avoids the disadvantages of non-aqueous formulations while retaining the required attributes

of a parenteral or oral formulation. The solution is stable, both chemically and physically; it is low in viscosity, therefore its syringability is excellent; it does not cause any irritation or tissue damage at the injection site; its taste is not objectionable upon oral administration; the solution is totally dilutable with water without precipitating the Ivermectin; the Ivermectin is rapidly absorbed; and the solution is produced at low cost.

The following illustrative non-limiting examples of aqueous formulations in accordance with the present invention are provided in order that the invention may be more fully understood.

EXAMPLE 1

Ivermectin Injectable Solution (10 mg/mL

Formula

MK-933		1.0%w/v
TWEEN 80		8%w/v
Glycerol Formal		20%w/v
Lidocaine		2%w/v
Benzyl Alcohol		1%v/v
Water for Injection	q.s.	100%v/v

pH adjusted to 6.2 using 1N HCl

Procedure

1. Dissolve MK-933 and lidocaine in TWEEN 80, glycerol formal, and benzyl alcohol.
2. Add water for injection equal to 80% of final volume.
3. Adjust pH of the solution to 6.2 using 1N HCl.
4. Adjust the solution to volume with water for injection.
5. Sterilize by autoclave or membrane filtration and package aseptically.

EXAMPLE 2

Ivermectin Injectable Solution (20 mg/mL

Formula

MK-933		2.0%w/v
TWEEN 80		12%w/v
Glycerol Formal		25%v/v
Benzyl Alcohol		3% v/v
Sodium Phosphate Dibasic - Anhydrous		0.1%w/v
Sodium Phosphate Monobasic - Monohydrate		0.9w/v
Water for Injection	q.s.	100%w/v

Procedure

1. Dissolve MK-933 in TWEEN 80, glycerol formal, and benzyl alcohol.
2. Disperse the buffer salts into the solution.
3. Add water for injection and agitate until a clear solution is obtained.
4. Adjust the solution to volume with water for injection.
5. Sterilize by autoclave or membrane filtration and package aseptically.

EXAMPLE 3

Ivermectin Oral Soluton (0.8 mg/mL

Formula

MK-933		0.08%w/v
TWEEN 80		8.0%w/v
Propylene Glycol		20%v/v
Benzyl Alcohol		3%v/v
Sodium Phosphate Dibasic - Anhydrous		0.1%w/v
Sodium Phosphate Monobasic - Monohydrate		0.9%w/v
Water, Purified	q.s.	100%w/v

Procedure

1. Dissolve MK-933 in TWEEN 80, propylene glycol, and benzyl alcohol.
2. Disperse the buffer salts into the solution.
3. Add purified water and agitate until a clear solution is obtained.
4. Adjust the solution to volume with purified water and package.

CLAIMS

1. A stabilized aqueous formulation comprising Ivermectin in a solution of a surface-active agent and water and including one or more water-miscible organic cosolvents suitable for parenteral or oral administration, and/or one or more substrates also suitable for parenteral or oral administration.

2. A formulation as claimed in Claim 1 that contains from 0.1 to 7.5% w/v of Ivermectin for parenteral administration or from 0.01 to 2.0% w/v of Ivermectin for oral administration; from 4 to 25% w/v of the surface-active agent; from 10 to 40% v/v of the cosolvent; and from 1 to 5% w/v of the substrate.

3. A formulation as claimed in Claim 1 or 2, in which the surface-active agent is a polyoxyethylated vegetable oil, polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate or polysorbate 80; the cosolvent is glycerol formal, propylene glycol, glycerine, or polyethylene glycol; and the substrate from benzyl alcohol, lidocaine, a paraben, or choline.

4. A formulation as claimed in Claim 1, in which a cosolvent is present but no substrate is included.

5. A formulation as claimed in Claim 4 containing from 0.1 to 7.5% w/v of Ivermectin for parenteral administrati n r from

0.01 to 2.0% w/v of Ivermectin for oral administration, from 4 to 25% w/v of a polyethylated vegetable oil, polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate or polysorbate 80; and from 10 to 40% v/v of glycerol formal, propylene glycol, glycerine or polyethylene glycol.

6. A formulation as claimed in Claim 1, in which a substrate is present but no cosolvent is included.

7. A formulation as claimed in Claim 6 comprising from 0.1 to 7.5% w/v of Ivermectin for parenteral administration or from 0.01 to 2.0% w/v of Ivermectin for oral administration; from 4 to 25% w/v of a polyoxyethylated vegetable oil, polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate or polysorbate 80; and from 1 to 5% w/v of one or more of benzyl alcohol, lidocaine, a paraben, or choline.

8. A process for preparing a stabilized aqueous formulation containing Ivermectin, which comprises dissolving Ivermectin in a surface-active agent containing one or both of (1) a cosolvent comprising one or more water-miscible organic solvents suitable for parenteral administration and (2) one or more of a substrate suitable for parenteral or oral administration; adding water to the thus prepared solution to make up the desired volume and adjusting the pH if necessary.

9. A process as claimed in Claim 8, in which the final solution has a pH adjusted to be in the range 6 to 6.5 and is a solution as claimed in Claim 2 or 3.

10. A process as claimed in Claim 9, in which the surface-active agent is polysorbate 80, the cosolvent is glycerol formal or propylene glycol and the substrate is one or both of benzyl alcohol or lidocaine.